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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KALLIS, RUSSELL	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/987,025	BORONAT ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5 and 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims an isolated nucleic acid molecule comprising a nucleic acid sequence encoding a 1-deoxy-D-xylulose 5-phosphate reductoisomerase found in *Arabidopsis*; an isolated polynucleotide comprising SEQ ID NO: 1; an isolated polynucleotide comprising a polynucleotide encoding a polypeptide of SEQ ID NO: 2; an isolated polynucleotide comprising a nucleotide sequence having at least 70% to 95% sequence identity to SEQ ID NO: 1; and a polynucleotide that hybridizes to SEQ ID NO: 1 under conditions of unspecified stringency.

Applicant teaches an isolated polynucleotide of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2

Applicant does not teach any other isolated polynucleotide other SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2 or any other polynucleotides hybridizing thereto.

Given the claim breadth and lack of guidance as discussed above, the specification does not provide an adequate written description of the claimed invention.

See *University of California V. Eli Lilly and Co.,* 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The court also addressed the manner by which genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* At 1406.

Given the failure of the DNA having at least 70% to 95% sequence identity to SEQ ID NO: 1; or the DNA that hybridizes to SEQ ID NO: 1 to be adequately described, methods of its use are also inadequately described. See Written Description Guidelines, Federal Register Vol. 66 No. 4, Friday January 5, 2001 "Notices", pages 1099-111.

Claims 21-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant broadly claims methods for increasing disease resistance in a plant, for increasing or decreasing isoprenoid content in a plant using contructs comprising DNA in either sense or antisense orientation, for increasing the non-mevalonate isoprenoid biosynthetic flux in plants transformed with an isolated polynucleotide comprising SEQ ID NO: 1, an isolated

polynucleotide comprising a nucleotide sequence encoding a polypeptide of SEQ ID NO: 2, an isolated polynucleotide comprising a nucleotide sequence having at least 70% to 95% sequence identity to SEQ ID NO: 1, or a polynucleotide that hybridizes to SEQ ID NO: 1 under conditions of unspecified stringency.

Applicant teaches isolation of SEQ ID NO: 1 encoding SQ ID NO: 2 from *Arabidopsis* by searching an EST database using an *E. coli* clone encoding a 1-deoxy-D-xylulose 5-phosphate reductoisomerase, RACE PCR of the 5' ends and sequencing of the completed EST clones.

Applicant does not teach isolation of any other sequence encoding a 1-deoxy-D-xylulose 5-phosphate reductoisomerase other than SEQ ID NO: 1 and does not teach any method of using the isolated polynucleotide of SEQ ID NO: 1 from *Arabidopsis*.

The phenotypic character expected from expression of a DNA construct often cannot be reliably predicted. In an example that demonstrates this all too common and unpredictable feature in the art, antisense expression of a polygalacturonase gene in transgenic tomato had no effect on fruit softening (Smith C. *et al.*; Nature 1988, 334: 724-726, p. 725).

Isolating DNA fragments using stringent hybridization conditions, does not always select for DNA fragments whose contiguous nucleotide sequence is the same or nearly the same as the probe. Fourgoux-Nicol et al (1999, Plant Molecular Biology 40 :857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at 65°C (page 859, left column, 2nd paragraph). Fourgoux-Nicol et al also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single

nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2).

Further, the isolation of isolation or manufacture of DNA sequences with a degree of identity to a target sequence introduces an element of unpredictability. The limitation is introduced in finding regions that would adequately enable either PCR amplification or southern hybridization and would entail using either degenerate primers or probes with limited homology and in recognizing conserved regions of class of polynucleotides encoding polypeptides with a common specific activity. Thus the screen for orthologous sequences would isolate many genes other than those of interest. The inherent unpredictability in isolation of a sequence with similar sequence identity encoding the same protein activity is illustrated in an example where a small number of changes to the coding region for a strict desaturase resulted in an enzyme with a hydroxylase activity and that a small number of changes to the coding region of a desaturase could account for the functional divergence seen across a range of enzymes involved in fatty acid metabolism (Broun P. *et al.* Science Vol. 282; 13 November 1998, pp. 1315-1317; Abstract lines 4-6 and p. 1317 column 1, lines 37-56).

Moreover, evidence for a non-limiting role for reductoisomerases in the non-mevalonic isoprenoid biosynthetic pathway in bacteria and plants suggests that altering the expression using antisense or sense of a reductoisomerase encoding gene would have no effect; particularly since the enzyme just upstream of the reductoisomerase in the mevalonic isoprenoid biosynthetic pathway has been shown to be limiting for isoprenoid flux. (Estevez J. *et al.* June 22, 2001; Vol.

276; No. 25, pp. 22901-22909 on page 22907 column 2, lines 27-38; and Rodriguez M. *et al.* The Plant Journal, 2001, vol. 27; No. 3, pp. 213-222 on page 219 column 1, lines 19-30).

In addition, the likelihood of enhancing disease resistance from transformation with a gene involved in disease resistance cannot be predicted. The constituitive expression of pathogenesis related proteins in transformed Tobacco resulted in plant with no alteration in phenotype and no affect upon the plant's susceptibility to infection with TMV or alfalfa mosaic virus (Linthorst H. *et al.* The Plant Cell, March 1989; Vol. 1; pp. 285-291; see Abstract).

Given the lack of guidance for isolating any other polynucleotide encoding a reductoisomerase other than SEQ ID NO: 2, or for producing plants transformed with varied sequence identity to SEQ ID NO: 1 in sense or antisense orientation or any other non-exemplified reductoisomerase genes in either sense or antisense orientation, or for making plants that show altered biosynthetic flux through the non-mevalonic pathway such that resistance to disease is impacted in any appreciable fashion, given the breadth of the claims and the unpredictability in the art, undue trail and error experimentation would be needed by one skilled in the art to isolate a multitude of non-exemplified reductoisomerase genes, or to evaluate the ability of a multitude of non-exemplified reductoisomerase genes to alter the phenotype of a multitude of transformed plant species. Therefore, the invention is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 21-24 and 36-39 are rejected under 35 U.S.C. 102(a) as being anticipated by Sato S. *et al.* (GenBank Accession number AB009053 submitted November 27, 1999 and described in attached sequence report).

Sato teaches the open reading frames of an *Arabidopsis* genomic clone comprising SEQ ID NO: 1 encoding a 1-deoxy-D-xylulose 5-phosphate reductoisomerase enzyme and inherently teaches a construct and host cell comprising said DNA. Thus the reference teaches all the limitations of the Claims 21-24.

Claims 22-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Burkhardt P. *et al.* (The Plant Journal, 1997; Vol. 11, No. 5; pp. 1071-1078).

The claims are broadly drawn to an isolated polynucleotide encoding an unspecified protein in part (g) of claims that recite an "isolated polynucleotide that hybridizes" to SEQ ID NO: 1 under conditions of unspecified stringency and duration; constructs, plant cells, and plants comprising said DNA that produce an isoprenoid compound of interest having altered or increased isoprenoid biosynthetic pathway activity.

Burkhardt teaches increased phytoene production in rice transformed with a DNA construct comprising phytoene synthase from daffodil. Thus, the reference teaches all the limitations of Claims 22-35.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Croteau *et al.* (U.S. Patent 6,281,017) in view of Sato *et al.* (GenBank Accession number AB009053 submitted November 27, 1997 and described in attached sequence report).

Applicant claims methods for modulating disease resistance in a plant, for increasing or decreasing isoprenoid content in a plant using contructs comprising DNA in either sense or antisense orientation, for increasing the non-mevalonate isoprenoid biosynthetic flux in plants transformed with an isolated polynucleotide comprising SEQ ID NO: 1, an isolated polynucleotide comprising a nucleotide sequence encoding a polypeptide of SEQ ID NO: 2, an isolated polynucleotide comprising a nucleotide sequence having at least 70% to 95% sequence identity to SEQ ID NO: 1, or a polynucleotide that hybridizes to SEQ ID NO: 1.

Croteau teaches an isolated DNA sequence encoding a 1-deoxy-D-xylulose 5-phosphate reductoisomerase enzyme from *Mentha x piperita* for use in enhancing the production of chlorophyll, terpenoids, phytoalexins, and carotenoids in a plant (column 11 lines 1-35), and antisense suppression of 1-deoxy-D-xylulose 5-phosphate reductoisomerase activity (column 20, lines 29-49).

Croteau does not teach the *Arabidopsis* polynucleotide sequence of SEQ ID NO: 1 encoding a 1-deoxy-D-xylulose 5-phosphate reductoisomerase enzyme of SEQ ID NO: 2.

The teachings of Sato are discussed supra.

It would have been obvious at the time of Applicant's invention to modify the invention of Croteau to include the *Arabidopsis* 1-deoxy-D-xylulose 5-phosphate reductoisomerase sequence taught by Sato. One of skill in the art would have been motivated by the knowledge common in the art that 1-deoxy-D-xylulose 5-phosphate reductoisomerase enzyme plant genes

are valuable materials for genetic engineering of plants to overproduce or restrict the production of carotenoids, terpenoids, chlorophyll, and phytoalexins using the methods taught by Corteau yielding a variety of beneficial and useful plants, and that one would have had a reasonable expectation of success of expressing genes in transformed plants and plant cells. Modulated disease resistance would have been an inherent property of the transformed plants, either due to the transgene or to its insertion in a gene conferring disease resistance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on Monday-Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding, or if the examiner cannot be reached as indicated above, should be directed to the receptionist, whose telephone number is (703) 308-0196.

Russell Kallis Ph.D.
February 1, 2003

DAVID T. FOX
PRIMARY EXAMINER
GROUP 180 1638